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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 08/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/955,216	BROWN ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,24 and 25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10, 24, 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

HC

DETAILED ACTION

1. Currently, claims 10, 24, and 25 are pending in the instant application. The rejections made under 35 USC 101 and 112, first paragraph with regard to enablement are maintained herein. To conform with current office policy, the rejection under 35 USC 112/first paragraph with regard to written description is being reinstated for the pending claims. Accordingly this action is made non final.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The rejection of claims 10, 24, and 25 under 35 USC 102(b) as being anticipated by Sigma catalogue is withdrawn in view of applicant's arguments at page 18.

Claim Rejections - 35 USC § 101

4. Claims 10, and 24-25 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility.

The claims are drawn to an isolated nucleic acid molecule comprising the nucleic acid sequence of SEQ ID NO: 7 (claim 10). Claims 24 and 25 are drawn to nucleic acid molecules that comprise a nucleic acid that shares between 98-100% identity with SEQ ID NO: 7 or it's complement. Claim 10 does not allow for internal variations within SEQ ID NO: 7 or it's complement, and encompasses putative genes, full open reading frames, fusion constructs and cDNAs. Claims 24, and 25, do allow for internal variations. Such claims further encompass

mutants, variants, and homologs from any plant, of these genes, full open reading frames, fusion constructs and cDNAs (see for example pages 41-42 of the specification which asserts that the enzymes or fragments of gibberellin pathway enzymes of the present invention are homologues of other plant gibberellin pathway enzymes).

The specification teaches that SEQ ID NO: 7 was identified from library CMz031 (Lib148) (Table A and p. 170). The specification teaches that the library-designated CMz031 was cDNA prepared from maize pollen tissue at a particular developmental stage (V10+, p. 170). The specification asserts that SEQ ID NO: 7 encodes a maize or soybean copalyl diphosphate synthase enzyme [and would presumably be used in the gibberellin pathway to obtain gibberellin], or a fragment thereof (p. 16, lines 15-17) and is therefore useful to identify and obtain homologues in both maize and non-maize plants (see pages 42-43, line 20 to line 4 respectively).

The utilities for the claimed nucleic acids stem from their potential ability; to encode copalyl diphosphate synthase; to be used as a probe, that is to hybridize to other nucleic acids to obtain the full length sequence of SEQ ID NO: 7, to obtain homologues, or to determine expression (see specification page 73); to be used to obtain promoters and other genetic elements associated with the claimed nucleic acid sequence (specification page 59); to determine the presence and/or identify of a polymorphism (specification page 60); and as a molecular marker for a desired trait (specification page 68).

Other than providing results of an alignment with SEQ ID NO 7, the specification provides no evidence that SEQ ID NO: 7 encodes a CPS, or that it was successfully used as a probe to obtain a functional CPS in plants (either a full length cDNA comprising SEQ ID NO: 7

and encoding a functional CPS or functional homologues in maize and non-maize plants) or to determine mRNA expression.

Such utilities are based upon homology/identity to experimentally known sequences of the cDNA for maize kaurene synthase A, also known as copalyl diphosphate synthase (g1576885, 03-Aug-1995; Table A and p. 42). CPS catalyzes the first committed step in diterpenoid biosynthesis leading to gibberellins in plants. It cyclizes gerenylgeranyl diphosphate (GGD) to copalyl diphosphate (CP). A sequence alignment revealed that nucleotides 60-470 of SEQ ID NO: 7 (SEQ ID NO: 7 is 470 nucleotides long) possessed 93.4% identity to nucleotides 2104-2512 of Zea mays kaurene synthase A (an1).

The asserted utilities are neither specific nor substantial because the disclosed uses (ie, use as a hybridization probe) are generally applicable to broad classes of this subject matter. In addition, further characterization of the claimed subject matter (for example, use to encode a peptide with catalytic function – see specification page 37, end of 4th full para) would be required to reasonably confirm a "real world" use, as evidenced by the teachings of the art as set forth below.

Firstly, it is known that for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence similarity results in an unpredictable and therefore unreliable correspondence between the claimed nucleotide and the indicated similar nucleotides of known function and therefore lacks support regarding utility. Several publications document the unpredictability of the relationship

between sequence and function. For example, Van de Loo et al (PNAS, vol. 92, pages 6743-6747 (1995) teaches that polypeptides of approximately 67% homology to a desaturases in Arabidopsis were found to be a hydroxylases once tested for activity. Seffernick et al (J. Bacteriol. Vol 183, pages 2405-2410; 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid identity catalyze two different reactions, deamination and dehalogenation. Broun et al (Science, vol. 282, pages 1315-1317, 1998) teaches that as few as four amino acid substitutions can convert an oleate 12 desaturase into a hydroxylase and as few as six amino acid substitutions can transform a hydroxylase into a desaturase. See also, [(Gerhold et al. BioEssays, vol. 18, n. 12, pp. 973-9814; 1996), (Wells et al. J. Leukocyte Biol., vol. 61, n. 5, pp. 545-550; 1997); and (Russell et al. J Molecular Biol., vol. 244, pp. 332-350; 1994)].

The art provides further evidence of unpredictability as to whether SEQ ID NO: 7 itself or whether the full cDNA (if one exists) that comprises SEQ ID NO: 7 will encode a functional enzyme. From the sequence alignment with An1, it appears that SEQ ID NO: 7 is only a partial fragment of a putative full length cDNA. The 93.4% similarity exists with the portion of the nucleic acid which encodes the extreme C terminal end of An1. The art, however, teaches that such a fragment of An1 would not be expected to have copalyl diphosphate synthase activity. Smith et al (Plant Physiol. 1998, pages 1411-1419) teaches an alignment of plant CPS's including An1 (see Figure 1), and teaches that truncation mutants revealed that once the enzyme was truncated up to a certain point on the N-terminus in pumpkin CmCPS1 and CmCPS2, that such enzymes lacked activity (see figure 1, inverted triangle and legend). If SEQ ID NO: 7 encodes a fragment of a functional CPS, it is no where near this N terminal point. Further, the

art provides reason to doubt whether a full length cDNA that comprises SEQ ID NO: 7 even exists, and if so, if it would encode a functional CPS or a pseudogene. Sakamoto et al (Plant Physiol. Vol. 134, pages 1642-1653, 2004) teaches that in rice, a number of CPS-like sequences were found, including one which turned out to be a non functional pseudogene (see table 1, OsCPS3). Sakamoto teaches that other homologues might have different functions than those for OsCPS1 and An1 (see page 1644, col. 2, last sentence of first full para). Sakamoto also teaches of the frequent presence of small pieces of CPS-like sequences in the rice genome (see page 1652, col. 1, last sentence of para 2). While the specification asserts that the nucleic acids of the specification encode a gibberellin pathway enzyme or "fragment thereof", it is unclear what use the "fragment" that SEQ ID NO: 7 appears to be, would have in any catalytic or enzymatic capacity given the teachings of the pre and post filing date art as noted above. The specification provides no evidence of any catalytic or enzymatic activity for a peptide encoded by SEQ ID NO: 7.

As previously noted, the specification also asserts that SEQ ID NO: 7 can be used to hybridize to another nucleic acid molecule (page 37, 4th full para; page 38-page 39), that sequences with less than 100% identity to SEQ ID NO: 7 could be used to hybridize to SEQ ID NO: 7 or it's complement (last para of page 39-page 41), to obtain homologues (page 43), and to be used as markers (pages 46-49).

The specification has provided no evidence of any successful use of SEQ ID NO: 7 for any of these purposes. As already noted, further experimentation would be required to reasonably confirm that SEQ ID NO: 7 would encode a peptide with any catalytic or enzymatic activity. The specification provides no evidence that the expression of SEQ ID NO: 7 is

associated with any particular phenotype or trait, such that no specific or substantial use for SEQ ID NO: 7 as a marker, or to determine mRNA expression, is apparent. Given the state of the post filing date art, it is reasonable to assume that more than one CPS exists in maize. Through mutational analysis, An1 has been shown to be a functional CPS in maize (see Bensen et al, The Plant Cell, vol. 7, pages 75-84, 1995). A homozygous deletion mutant of An1 accumulated ent-kaurene to 20% of wild type levels, indicating the presence of isoenzymes (see page 436 of Hedden & Kamiya, Ann. Rev. Plant Physio. Plant Mol. Biol. 1997, pages 431-460, 1997). A second putative CPS homologue has been isolated in maize (termed An2), however, to date, it's function or activity have not been confirmed. Sequence analysis has revealed that it does not comprise SEQ ID NO: 7. Therefore, it appears that maize could contain a number of putative CPS-like sequences (see specification Table A, page 210). However, as evidenced by the post filing date art of Sakamoto, there is reason to doubt whether all of these sequences are associated with a full length nucleic acid which encodes a functional enzyme. Sakamoto teaches that one possible explanation for the presence of CPS like sequences which do not function in gibberellin biosynthesis is that multiple copies are deleterious for growth and development, as discussed by Aubourg with regard to Arabidopsis (see page 1652, end of col. 1). Sakamoto acknowledges the need for further experimentation in the form of biochemical studies to confirm such. In the instant case, further experimentation would be required to confirm a "real world" use for SEQ ID NO: 7, either as a marker (that is, the specification provides no evidence that it is a marker for any phenotype or trait), or as a nucleic acid itself to be detected (the specification has provided no evidence that the detection of SEQ ID NO: 7 itself provides any specific, substantial or real world use), for example to detect a cDNA or gene, in gene mapping, or for gene expression (that

is, the specification provides no evidence that SEQ ID NO: 7 is part of a full length cDNA or gene encoding a functional CPS, or that SEQ ID NO: 7 can be used to detect gene expression which would result in any useful information).

The possible use of SEQ ID NO: 7 as a probe to isolate or detect homologues in maize and non maize plants is dependent on the hybridization conditions used for the analysis. Depending on the conditions of stringency of hybridization and wash, for example a lowering of stringency, there would be a greater likelihood that a large number of different nucleic acids would be detected (that is, nucleic acids encoding different proteins with different functions). There would be no reasonable expectation that all nucleic acids detected would have the same function, (or as evidenced by the teachings of the art: that the sequences would have any function), or what that function would be. Further experimentation would be required to reasonably confirm the "real world" use for detection or isolation of these nucleic acids. In such case, the use of SEQ ID NO: 7 would be like that of any uncharacterized EST with no specific, substantial or real world use.

With regard to the use of SEQ ID NO: 7 to detect polymorphisms, the specification does not teach any polymorphism in SEQ ID NO: 7, or one that could be identified with SEQ ID NO: 7. If the skilled artisan determines that a polymorphism in SEQ ID NO: 7 is present, the skilled artisan would not know how to use the information because the specification provides no teaching of any polymorphism, let alone any information that would be apparent based on the presence or absence of the polymorphism. The specification provides no association between any useful trait or phenotype and any polymorphism in SEQ ID NO: 7, or that could be identified with SEQ ID NO: 7. Such use, is therefore not considered a substantial utility. This lack of

association can only be remedied, if such an association with any phenotype even exists for the instantly claimed nucleic acids, by further research. It is also unknown what such research may or may not find regarding the instantly claimed nucleic acid molecules. This supports the lack of a currently available utility for the instantly claimed invention. Even if the polymorphism is determined, the presence or absence of a polymorphism does not have a clear utility. Polymorphisms are natural variations within sequences which themselves may not have any meaningful use. Therefore, determining whether the claimed nucleic acids have or do not have a polymorphism would require determining whether there was a polymorphism within such a sequence and then determining how to use this information.

With regard to the assertion that SEQ ID NO: 7 can be used to isolate promoters or other regulatory elements, as set forth above, there is no evidence in the specification that a full length gene comprising SEQ ID NO: 7 exists, whereas the art provides evidence that plants can contain multiple CPS like sequences that are either CPS like fragments, or pseudogenes. As such, it is not known whether or not a promoter for SEQ ID NO: 7 exists. With regard to the use for the claimed nucleic acid with regard to providing a useful starting point for a chromosomal walk, the specification fails to demonstrate that any of the claimed nucleic acid molecules would be useful in obtaining successful result from such search

As noted in Brenner v. Manson, 383 U.S. 519, 535-536 (1996), "Congress intended that no patents be granted on a chemical compound whose sole "utility" consists of its potential role as an object of use-testing... a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion". The specification provides no evidence that SEQ ID NO: 7 encodes a CPS, or that it was successfully used as a probe to obtain a functional

CPS in plants (either a full length cDNA comprising SEQ ID NO: 7 and encoding a functional CPS or functional homologues in maize and non-maize plants) or to determine mRNA expression or that any polymorphisms exist, and if so, what they would be used for.

Response to Arguments

5. The response traverses the rejection. The arguments begin at page 6 of the response. At page 6, although acknowledging the citations made with regard to publications, the response asserts that "the examiner provides no support to show that SEQ ID NO: 7 does not function as described by the specification". This argument has been thoroughly reviewed but was not found persuasive as the previous office action provided analysis of the art with regard to CPS enzymes. The specification bases its assertion that SEQ ID NO: 7 encodes a maize CPS based on homology/identity to a known CPS. In assessing whether one of skill in the art would predictably establish such function, the office action provided a general overview of the art with regard to the predictability of basing function of a protein solely on homology/identity analysis with a known sequence (office action para bridging page 5-6). The office action then provides the state of the knowledge in the art with regard to CPS enzymes (office action page 6). As stated in the office action, using the specification's basis of homology/identity, one of skill in the art would not reasonably predict that SEQ ID NO 7 encoded a functional CPS enzyme because Smith teaches that in An1 and CPS's found in pumpkin, enzyme activity is found at the N-terminal portion of the enzyme, whereas SEQ ID NO 7 aligns to portion of the nucleic acid encoding the extreme C-terminal end of An1. With regard to the specification's assertion that SEQ ID NO: 7 encodes a CPS fragment, again, citing publications, the office action set forth that

although more than one CPS could exist in maize, the art teaches that different plant species possess a number of CPS like pseudogenes with no activity. Therefore, contrary to the response's assertion, the office action has provided extensive support, in the form of publications representing the current state of the art with regard to CPS enzymes, as well as scientific reasoning with regard to such publications. Further experimentation would be required of the skilled artisan to reasonably confirm the function of a peptide encoded by SEQ ID NO: 7, or to confirm whether SEQ ID NO: 7 encodes a fragment of a functional CPS. This analysis is based on the state of the art with regard to CPS enzymes. The only evidence provided by the specification, is based on sequence identity, which is unpredictable, as evidenced by the teachings in the art. In the instant case, the office action used sound scientific reasoning based on the teachings in the art and the state of the art to rebut the assertion made in the specification (referring to arguments made in first full para of page 7 of response).

The response asserts that the disclosed utilities in the specification are directly analogous to the utilities of a microscope. This argument has been reviewed but is not persuasive because the microscope provides information to the scientist which is automatically useful. For example, the microscope may be used for identification and differentiation between gram-positive and gram-negative bacteria. The differentiation of bacteria facilitates in the administration of proper antibiotics. For example, if the microscope is used to determine whether Staph is present or whether Strep is present provides valuable information to the scientist and/or doctor for treating patients. The response further asserts that the asserted use of the claimed nucleic acid to detect the presence or absence of polymorphisms is nor more legally insufficient than using a gas chromatograph to analyze the chemical composition of a gas. This argument has been

thoroughly reviewed but was not found persuasive. A gas chromatograph is well known to be useful for detection of toxic material, for example. These uses are well known and beneficial in that results are already determined which are useful for at least one analysis type. The instant invention, however, provides no information to this extent. The specification does not teach if the sequence contains or lacks any specific polymorphism. If the scientist determines that a polymorphism in SEQ ID NO: 7 is present or not, the scientist does not know how to use this information. Such use, is therefore not considered a substantial utility.

The response asserts that one skilled in the art could ascertain uses such as a specific or substantial phenotypic change or predisposition based on the specification's disclosure and tools such as BLASTX, and that such a disclosure is not necessary for the disclosed utilities as probes or to detect the presence of polymorphisms. This argument has been thoroughly reviewed but was not found persuasive. As noted above, the specification does not provide any evidence that SEQ ID NO: 7 is a fragment of a functional CPS. Further, the specification does not teach whether or not SEQ ID NO: 7 contains, or does not contain, any specific polymorphisms. The arguments as to ascertaining the uses tools available to practitioners in the art highlights the need for further experimentation to reasonably confirm a real world use for the claimed sequences. It is not known if SEQ ID NO: 7 does or does not contain any specific polymorphism, therefore further experimentation would be required to determine if SEQ ID NO: 7 could be used indicate a common heritage with any other plant.

With regard to the response's arguments concerning credibility, the credibility of the asserted uses has not been challenged. It is acknowledged that polymorphism analysis, for example, are credible utilities, but that a lack of utility still exists if there is no well established

utility or either a specific or substantial utility as is the situation for the instantly claimed invention. For these reasons and the reasons already made of record, the rejection is maintained.

Claim Rejections - 35 USC § 112

6. Claims 10, 24, and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making the nucleic acid sequence of SEQ ID NO: 7 or it's complement, does not reasonably provide enablement for making or using the nucleic acids encompassed by the broad scope of claims 10, 24, and 25. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Additionally, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above in section 5, one skilled in the art clearly would not know how to use the claimed invention.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are drawn to an isolated nucleic acid molecule comprising the nucleic acid sequence of SEQ ID NO: 7 (claim 10). Claims 24 and 25 are drawn to nucleic acid molecules that comprise a nucleic acid that shares between 98-100% identity with SEQ ID NO: 7 or it's complement. Claim 10 does not allow for internal variations within SEQ ID NO: 7 or it's complement, and encompasses putative genes, full open reading frames, fusion constructs and cDNAs. Claims 24, and 25, do allow for internal variations. Such claims further encompass mutants, variants, and homologs from any plant, of these genes, full open reading frames, fusion constructs and cDNAs (see for example pages 41-42 of the specification which asserts that the enzymes or fragments of gibberellin pathway enzymes of the present invention are homologues of other plant gibberellin pathway enzymes). However, the specification provides insufficient guidance for the skilled artisan to make or use the broad scope of nucleic acids encompassed by the instantly pending claims.

The specification teaches that SEQ ID NO: 7 was identified from library CMz031 (Lib148) (Table A and p. 170). The specification teaches that the library-designated CMz031 was cDNA prepared from maize pollen tissue at a particular developmental stage (V10+, p. 170). The specification asserts that SEQ ID NO: 7 encodes a maize or soybean copalyl diphosphate synthase enzyme [and would presumably be used in the gibberellin pathway to obtain gibberellin], or fragment thereof (p. 16, lines 15-17) and is therefore useful to identify and obtain homologues in both maize and non-maize plants (see pages 42-43, line 20 to line 4 respectively). The uses set forth by the specification for SEQ ID NO: 7 are based upon homology/identity to experimentally known sequences of the cDNA for maize kaurene synthase A, also known as copalyl diphosphate synthase (g1576885, 03-Aug-1995; Table A and p. 42).

CPS catalyzes the first committed step in diterpenoid biosynthesis leading to gibberellins in plants. It cyclizes gerenylgeranyl diphosphate (GGD) to copalyl diphosphate (CP). A sequence alignment revealed that nucleotides 60-470 of SEQ ID NO: 7 (SEQ ID NO: 7 is 470 nucleotides long) possessed 93.4% identity to nucleotides 2104-2512 of Zea mays kaurene synthase A (an1). However, the specification provides no evidence that SEQ ID NO: 7 encodes a CPS, or that it was successfully used as a probe to obtain a functional CPS in plants (either a full length cDNA comprising SEQ ID NO: 7 and encoding a functional CPS or functional homologues in maize and non-maize plants), or to determine mRNA expression, or that it can be used as a marker, or that it contains or does not contain any specific polymorphism.

Given the state of the art and the unpredictability of the art as set forth below, it would require undue experimentation for the skilled artisan to make or use the broad scope of nucleic acids encompassed by the claims.

Due to the term "comprising", all of the claims encompass the full length gene and cDNA sequences that comprise SEQ ID NO: 7 or its complement. However, the art provides evidence of unpredictability as to whether SEQ ID NO: 7 itself or whether the full cDNA (if one exists) that comprises SEQ ID NO: 7 will encode a functional enzyme with copalyl diphosphate synthase activity. From the sequence alignment with An1, it appears that SEQ ID NO: 7 is only a partial fragment of a putative full length cDNA. The 93.4% similarity exists with the portion of the nucleic acid which encodes the extreme C terminal end of An1. The art, however, teaches that such a fragment of An1 would not be expected to have copalyl diphosphate synthase activity. Smith et al (Plant Physiol. 1998, pages 1411-1419) teaches an alignment of plant CPS's including An1 (see Figure 1), and teaches that truncation mutants revealed that once the enzyme

was truncated up to a certain point on the N-terminus in pumpkin CmCPS1 and CmCPS2, that such enzymes lacked activity (see figure 1, inverted triangle and legend). If SEQ ID NO: 7 encodes a fragment of a functional CPS, it is no where near this N terminal point. Further, the art provides evidence of unpredictability as to whether a full length cDNA or gene that comprises SEQ ID NO: 7 exists, and if so, if it would encode a functional CPS or a pseudogene. Sakamoto et al (Plant Physiol. Vol. 134, pages 1642-1653, 2004) teaches that in rice, a number of CPS-like sequences were found, including one which turned out to be a non functional pseudogene (see table 1, OsCPS3). Sakamoto teaches that other homologues might have different functions than those for OsCPS1 and An1 (see page 1644, col. 2, last sentence of first full para). Sakamoto also teaches of the frequent presence of small pieces of CPS-like sequences in the rice genome (see page 1652, col. 1, last sentence of para 2). Therefore, given the teachings of the art, it would require undue experimentation to make the nucleic acids encompassed by the claims. While the specification generally teaches how to use nucleic acid sequences as hybridization probes, and while SEQ ID NO: 7 (or its complement) could be used to isolate a full length sequence which comprises SEQ ID NO: 7 (or its complement), there is reason to doubt whether such a full length sequence exists. The teachings of the specification provide one of skill in the art with a teaching of how to find nucleic acids that would fall within the scope of the claims. Such is not a teaching of the combination of nucleotide bases that would encode a copalyl diphosphate synthase enzyme comprising SEQ ID NO: 7. Therefore, given the lack of guidance from the specification and the unpredictability of the art, undue experimentation would be required for the skilled artisan to make a full length gene or cDNA sequence comprising SEQ ID NO: 7 which encoded copalyl diphosphate synthase.

Additionally, claims 24, and 25 encompass homologues and mutants of SEQ ID NO: 7 and sequences comprising SEQ ID NO: 7, that is full length gene or cDNA. However, it is known that for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence similarity results in an unpredictable and therefore unreliable correspondence between the claimed nucleotide and the indicated similar nucleotides of known function and therefore lacks support regarding enablement. Several publications document the unpredictability of the relationship between sequence and function. For example, Van de Loo et al (PNAS, vol. 92, pages 6743-6747 (1995) teaches that polypeptides of approximately 67% homology to a desaturases in Arabidopsis were found to be hydroxylases once tested for activity. Seffernick et al (J. Bacteriol. Vol 183, pages 2405-2410; 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid identity catalyze two different reactions, deamination and dehalogenation. Broun et al (Science, vol. 282, pages 1315-1317, 1998) teaches that as few as four amino acid substitutions can convert an oleate 12 desaturase into a hydroxylase and as few as six amino acid substitutions can transform a hydroxylase into a desaturase. See also, [(Gerhold et al. BioEssays, vol. 18, n. 12, pp. 973-9814; 1996), (Wells et al. J. Leukocyte Biol., vol. 61, n. 5, pp. 545-550; 1997); and (Russell et al. J Molecular Biol., vol. 244, pp. 332-350; 1994)]. The specification fails to teach which specific nucleotides can be altered by the skilled artisan without altering the function of the putative CPS encoded by SEQ ID NO: 7. Each variation results in a new and independent sequence that does not reliably result in similar or identical activity of the encoded

peptide, as evidenced by the teachings of the art. Therefore, given the lack of guidance from the specification and the unpredictability of the art, undue experimentation would be required for the skilled artisan to make homologues and mutants of SEQ ID NO: 7 or sequences comprising SEQ ID NO: 7, as is encompassed by the claims.

With regard to use of SEQ ID NO: 7 and homologues of SEQ ID NO: 7 (encompassed by claims 24, and 25), as noted above, SEQ ID NO: 7 appears to be a partial fragment of a putative CPS. This fragment does not appear to encode a peptide with any copalyl diphosphate synthase activity. The potential use for SEQ ID NO: 7 is not limited to its ability to encode a peptide, however. The specification also asserts that SEQ ID NO: 7 can be used to hybridize to another nucleic acid molecule (page 37, 4th full para; page 38-page 39), that sequences with less than 100% identity to SEQ ID NO: 7 could be used to hybridize to SEQ ID NO: 7 or it's complement (last para of page 39-page 41), to obtain homologues (page 43), and to be used as markers (pages 46-49). However, the specification has provided no evidence of any successful use of SEQ ID NO: 7 for any of these purposes. The specification provides no evidence that the expression of SEQ ID NO: 7 is associated with any particular phenotype or trait, such that no use for SEQ ID NO: 7 as a marker, or to determine mRNA expression, is apparent. Accordingly, even if SEQ ID NO: 7 were to contain a polymorphism, the skilled artisan would not be able to use the polymorphism information in any way other than to determine what effect it might have on a plant phenotype transformed with the nucleic acid of SEQ ID NO: 7. Given the state of the post filing date art, it is reasonable to assume that more than one CPS exists in maize. Through mutational analysis, An1 has been shown to be a functional CPS in maize (see Bensen et al, vol. 7, pages 75-84, 1995). A homozygous deletion mutant of An1 accumulated ent-kaurene to 20%

of wild type levels, indicating the presence of isoenzymes (see page 436 of Hedden & Kamiya, Ann. Rev. Plant Physio. Plant Mol. Biol. 1997, pages 431-460, 1997). A second putative CPS homologue has been isolated in maize (termed An2), however, to date, its function or activity have not been confirmed. Sequence analysis has revealed that it does not comprise SEQ ID NO: 7. Therefore, it appears that maize could contain a number of putative CPS-like sequences (see specification Table A, page 210). However, as evidenced by the post filing date art of Sakamoto, there is reason to doubt whether all of these sequences are associated with a full length nucleic acid which encodes a functional enzyme. Sakamoto teaches that one possible explanation for the presence of CPS like sequences which do not function in gibberellin biosynthesis is that multiple copies are deleterious for growth and development, as discussed by Aubourg with regard to Arabidopsis (see page 1652, end of col. 1). Sakamoto acknowledges the need for further experimentation in the form of biochemical studies to confirm such. In the instant case, further unpredictable experimentation would be required to determine how to use SEQ ID NO: 7 as a marker (that is, the specification provides no evidence that it is a marker for anything). The possible use of SEQ ID NO: 7 as a probe to isolate or detect homologues in maize and non maize plants is dependent on the hybridization conditions used for the analysis. Depending on the conditions of stringency of hybridization and wash, for example a lowering of stringency, there would be a greater likelihood that a large number of different nucleic acids would be detected (that is, nucleic acids encoding different proteins with different functions). There would be no reasonable expectation that all nucleic acids detected would have the same function, (or as evidenced by the teachings of the art: that the sequences would have any function), or what that function would be. Given that the ability of two sequences to hybridize to each other is based on

their nucleic acid structure, which does not necessarily correlate to any predictably similar function for the peptides encoded by such nucleic acids, further experimentation would be required to determine a use for the nucleic acids that would hybridize to SEQ ID NO: 7 (complement) or homologues of SEQ ID NO: 7 (as encompassed by claims 24 and 25).

Response to Arguments

7. The response traverses the rejection. The response asserts that the "make and test" quantum of experimentation is reduced by extensive knowledge and the teachings of the specification which sets forth nucleic acid molecules and methods of use in the production of transformed cells and plants. The response asserts that with regard to the second and third Wands criteria, the specification provides evidence of sequence identity and hybridization conditions and discusses the use of the claimed nucleic acids to encode a CPS or fragment and also discusses the use of the claimed nucleic acid to isolate additional sequences within a genome. These arguments have been thoroughly reviewed but were not found persuasive. The specification provides no evidence that a peptide encoding SEQ ID NO: 7 has CPS activity, nor does the specification provide any guidance as to any active site encoded by SEQ ID NO: 7 or what conservative substitutions could be made. Further, the art provides strong evidence to suggest that SEQ ID NO: 7 does not encode a peptide with CPS activity, and provides evidence of unpredictability as to whether a full length gene or cDNA comprising SEQ ID NO: 7 exists. Additionally, the possible use of SEQ ID NO: 7 as a probe to isolate or detect homologues in maize and non maize plants is dependent on the hybridization conditions used for the analysis. Depending on the conditions of stringency of hybridization and wash, for example a lowering of

stringency, there would be a greater likelihood that a large number of different nucleic acids would be detected (that is, nucleic acids encoding different proteins with different functions). There would be no reasonable expectation that all nucleic acids detected would have the same function, (or as evidenced by the teachings of the art: that the sequences would have any function), or what that function would be. Given that the ability of two sequences to hybridize to each other is based on their nucleic acid structure, which does not necessarily correlate to any predictably similar function for the peptides encoded by such nucleic acids, further experimentation would be required to determine a use for the nucleic acids that would hybridize to SEQ ID NO: 7 (complement) or homologues of SEQ ID NO: 7 (as encompassed by claims 24 and 25).

With regard to the response's arguments concerning the 4^{th}, 5^{th}, 6^{th} and 7^{th} Wands factors, the specification has provided general teachings of hybridization analysis to isolate or detect other nucleic acid sequences. However, such represent teachings of how to find embodiments that are encompassed by the broad scope of the claimed nucleic acids. In the instant case, the specification provides no evidence that a peptide encoding SEQ ID NO: 7 has CPS activity. Further, the art provides evidence to suggest that SEQ ID NO: 7 does not encode a peptide with CPS activity, and provides evidence of unpredictability as to whether a full length gene or cDNA comprising SEQ ID NO: 7 exists, regarding CPS fragments. Unpredictable trial and error experimentation would be required to make and use the broad scope of nucleic acid molecules, genes, full open reading frames, fusion constructs, and cDNAs (claim 10) with or without CPS activity as well as mutants, variants, and homologs from any plant, of these genes, full open reading frames, fusion constructs and cDNAs (claims 24 and 25), encompassed by the

claims. The use of sequence identity does not remedy such trial and error experimentation, given the unpredictability of SEQ ID NO: 7 encoding a CPS or fragment, as taught in the art. With regard to evidentiary burden, applicants are directed to evidence provided in teachings of the art and analysis of the teachings in the specification, as set forth above and in the previous office action. For these reasons and the reasons already made of record, the rejection is maintained.

8. Claims 10, 24 and 25 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to an isolated nucleic acid molecule comprising the nucleic acid sequence of SEQ ID NO: 7 (claim 10). Claims 24 and 25 are drawn to nucleic acid molecules that comprise a nucleic acid that shares between 98-100% identity with SEQ ID NO: 7 or it's complement. Claim 10 does not allow for internal variations within SEQ ID NO: 7 or it's complement, and encompasses putative genes, full open reading frames, fusion constructs and cDNAs. Claims 24, and 25, do allow for internal variations. Such claims further encompass mutants, variants, and homologs from any plant, of these genes, full open reading frames, fusion constructs and cDNAs (see for example pages 41-42 of the specification which asserts that the enzymes or fragments of gibberellin pathway enzymes of the present invention are homologues of other plant gibberellin pathway enzymes). The specification has only provided the sequence of SEQ ID NO: 7, but has provided no evidence that SEQ ID NO: 7 encodes a copalyl diphosphate synthase. The teachings of the art and a sequence alignment for SEQ ID NO: 7 provide strong

evidence that SEQ ID NO: 7 does not encode a peptide with copalyl diphosphate synthase activity.

Alignment studies with the An1 (CPS) gene in maize and SEQ ID NO: 7 suggest that SEQ ID NO: 7 is only a partial fragment of a putative full length cDNA. The 93.4% similarity exists with the portion of the nucleic acid which encodes the extreme C terminal end of An1. The art, however, teaches that such a fragment of An1 would not be expected to have copalyl diphosphate synthase activity. Smith et al (Plant Physiol. 1998, pages 1411-1419) teaches an alignment of plant CPS's including An1 (see Figure 1), and teaches that truncation mutants revealed that once the enzyme was truncated up to a certain point on the N-terminus in pumpkin CmCPS1 and CmCPS2, that such enzymes lacked activity (see figure 1, inverted triangle and legend). If SEQ ID NO: 7 encodes a fragment of a functional CPS, it is no where near this N terminal point. Additionally, Sakamoto et al (Plant Physiol. Vol. 134, pages 1642-1653, 2004) teaches that in rice, a number of CPS-like sequences were found, including one which turned out to be a non functional pseudogene (see table 1, OsCPS3). Sakamoto teaches that other homologues might have different functions than those for OsCPS1 and An1 (see page 1644, col. 2, last sentence of first full para). Sakamoto also teaches of the frequent presence of small pieces of CPS-like sequences in the rice genome (see page 1652, col. 1, last sentence of para 2). Thus, it is not clear as to whether a full length gene or cDNA that comprises SEQ ID NO: 7 would encode a functional CPS or a pseudogene.

The genus of nucleic acids encompassed by the claims includes any nucleic acid that comprises a sequence which shares between 98-100% sequence identity with SEQ ID NO: 7 or it's complement. This genus therefore encompasses putative genes, full open reading frames,

fusion constructs and cDNAs and mutants, variants, and homologs from any plant, of these genes, full open reading frames, fusion constructs and cDNAs. However, the specification has only taught the sequence of SEQ ID NO: 7, which appears to be a partial structure. As evidenced above, SEQ ID NO: 7 does not appear to encode a peptide with CPS activity and the specification has provided no evidence that SEQ ID NO: 7 or a sequence comprising SEQ ID NO: 7 encodes a functional enzyme. As such, the disclosure of SEQ ID NO: 7 is not representative of the putative full length genes, open reading frames, cDNA, mutants, variants or homologs which are encompassed by the claimed invention. Further, although the level of skill in the art is high, the specification, other than generally disclosing methods of site directed mutagenesis, making fusion peptides, etc, provides no description or guidance as to how to alter or construct a sequence comprising or hybridizing to SEQ ID NO: 7 which encodes an active enzyme. No teaching is provided on how to specifically manipulate SEQ ID NO: 7 to obtain a sequence which encodes a copalyl diphosphate synthase. Claims 24 and 25 encompass sequences with variations in comparison to SEQ ID NO: 7. As such, each member of the claimed genus does not contain the same structural feature. For those members that do contain SEQ ID NO: 7 or its complement, it does not appear that the peptide encoded by SEQ ID NO: 7 has enzymatic activity. As such, no structure-function correlation is present with regard to the structural feature of SEQ ID NO: 7 and the genus of nucleic acids encompassed by the claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NOS: 7 an its complement, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and proteins with copalyl diphosphate synthase activity they encode, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-

0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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8/15/05